LORD BISSELL BROOK LLP
ATTORNEYS AT LAW

115 S. LASALLE STREET | CHICAGO, ILLINOIS 60603-3901
312.443.0700 | 312.443.0336 FAX | WWW.LORDBISSELL.COM

December 23, 2004

Michael J. Gaertner
312.443.1722
Fax: 312.896.6722
mgaertner@lordbissell.com

Sara Ann Lufrano
Registered Patent Attorney
312.443.0495
Fax: 312.896.6495
slufrano@lordbissell.com

Via Overnight Courier

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane
Room 1061
Rockville, Maryland 20852

CITIZEN PETITION

REQUEST FOR IMMEDIATE RECALL OF ALL METHACHOLINE CHLORIDE PRODUCTS IN VIOLATION OF 21 U.S.C. §§ 331, 352, 355(a) AND A STOP TO ALL FURTHER VIOLATIONS OF 21 U.S.C. §§ 331, 352, 355(a) BY PRODUCTS CONTAINING METHACHOLINE CHLORIDE

On behalf of Methapharm Inc. ("Methapharm"), the undersigned submits this Petition under 21 U.S.C. §§ 331, 352, 355(a), Guidance for FDA Staff and Industry, Compliance Policy Guides Manual § 460.200 ("CPG"), 21 C.F.R. §§ 10.25(a) and 10.30, to request the Commissioner of Food and Drugs ("FDA" or "the Agency") to immediately take the following action:

- Order all non-FDA-approved producers of dosage form methacholine chloride listed at Tab 1 ("unapproved formulators") to stop introducing into interstate commerce any methacholine chloride without an approval from FDA under 21 U.S.C. §§ 355(b) or (j) in violation of 21 U.S.C. § 355(a);
- Order all unapproved formulators to stop introducing into interstate commerce any methacholine chloride that is misbranded in violation of 21 U.S.C. § 352;
- Order all unapproved formulators to stop engaging in the following acts in an attempt to circumvent 21 U.S.C. § 352 and 21 U.S.C. § 355(b) and (j) under the guise of compounding:
    1) "Compounding" methacholine chloride without first receiving a valid prescription;

2004P.0562 CP1

2) "Compounding" finished methacholine chloride from bulk methacholine chloride that is not a component of any FDA approved drug without an FDA sanctioned investigational new drug application (IND) in accordance with 21 U.S.C. § 355(i) and 21 CFR § 312;
3) Receiving, storing or using methacholine chloride before obtaining written assurance from the supplier that each lot of methacholine chloride has been made in an FDA-registered facility;
4) Receiving, storing or using methacholine chloride not guaranteed or otherwise determined to meet official compendia requirements;
5) "Compounding" methacholine chloride that is essentially a copy of Methapharm's Provocholine® (methacholine chloride) 100 mg/vial powder for solution, approved by FDA under NDA No. 19-193.

- Order all tech grade suppliers of bulk methacholine chloride listed at Tab 2 ("tech grade suppliers") to stop supplying non-FDA-approved bulk methacholine chloride to unapproved formulators and knowingly contributing to and inducing the unapproved formulators in the above violations;
- Order all tech grade suppliers and unapproved formulators to refrain from any recurrence of the above violations;
- Order a recall of all methacholine chloride containing products that are in violation as set forth above.

A. Action Requested.

Methapharm requests that FDA immediately take the following action:

- Order all unapproved formulators to stop introducing into interstate commerce any methacholine chloride without an approval from FDA under 21 U.S.C. §§ 355(b) or (j) in violation of 21 U.S.C. § 355(a);
- Order all unapproved formulators to stop introducing into interstate commerce any methacholine chloride that is misbranded in violation of 21 U.S.C. § 352;
- Order all unapproved formulators to stop engaging in the following acts in an attempt to circumvent 21 U.S.C. § 352 and 21 U.S.C. §§ 355(b) and (j) under the guise of compounding:
    1) "Compounding" methacholine chloride without first receiving a valid prescription;

2) "Compounding" finished methacholine chloride from bulk methacholine chloride that is not a component of any FDA approved drug without an FDA sanctioned investigational new drug application (IND) in accordance with 21 U.S.C. § 355(i) and 21 CFR § 312;
3) Receiving, storing or using methacholine chloride before obtaining written assurance from the supplier that each lot of methacholine chloride has been made in an FDA-registered facility;
4) Receiving, storing or using methacholine chloride not guaranteed or otherwise determined to meet official compendia requirements;
5) "Compounding" methacholine chloride that is essentially a copy of Methapharm's Provocholine® (methacholine chloride) 100 mg/vial powder for solution, approved by FDA under NDA No. 19-193.

- Order all tech grade suppliers to stop supplying non-FDA approved methacholine chloride to unapproved formulators and knowingly contributing to and inducing the unapproved formulators in the above violations;
- Order all tech grade suppliers and unapproved formulators to refrain from any recurrence of the above violations;
- Order a recall of all methacholine chloride containing products that are in violation as set forth above

Methapharm will treat a failure by the Agency to respond as a final Agency decision, and will immediately seek all available administrative and/or legal remedies.

B. Statement Of Grounds.

Factual Background

Methacholine Chloride

The drug at issue here is methacholine chloride, a cholinergic bronchoconstriction agent, used in conducting asthma testing. The only form of methacholine chloride that has been approved by FDA is Methapharm's Provocholine® 100 mg/vial powder to be administered in solution by inhalation, approved by FDA under NDA No. 19-193 on October 31, 1986.

All allegations that follow are based on information and belief.

Tech grade suppliers (Tab 2) are supplying large quantities of bulk methacholine chloride to pharmacies and other organizations which are then using that bulk methacholine chloride to formulate dosage form methacholine chloride that is administered to patients. The bulk methacholine chloride sold by the tech grade suppliers and used in these formulations is manufactured by facilities that have not submitted a Drug Master File to FDA describing the components, processes and controls used to manufacture the bulk methacholine chloride. The facilities that manufacture this bulk methacholine chloride have not been subject to FDA inspection relating to their manufacture of methacholine chloride. The bulk methacholine chloride produced by these manufacturers and sold by the tech grade suppliers is not a component of any FDA-approved drug or FDA-sanctioned IND. The tech grade suppliers are selling very large quantities of bulk methacholine chloride to the unapproved formulators.

The unapproved formulators (Tab 1) consist of pharmacies and other organizations that use bulk methacholine chloride purchased from the tech grade suppliers to formulate dosage form methacholine chloride. The unapproved formulators are purchasing very large quantities of bulk methacholine chloride from the tech grade suppliers. The unapproved formulators are producing a very substantial volume of dosage form methacholine chloride. The unapproved formulators are using the bulk methacholine chloride primarily, if not exclusively, to produce dosage form methacholine chloride to be administered to patients and not for research and development purposes. Many of these unapproved formulators administer only their self-manufactured unapproved drug to patients and do not even offer FDA approved methacholine chloride to patients.

The unapproved formulators are attempting to circumvent FDA statutes and regulations applicable to the manufacture and sale of New Drugs by producing dosage form methacholine chloride under the guise of "compounding." The unapproved formulators' large-scale production of non-FDA-approved methacholine chloride does not qualify as pharmacy compounding because, *inter alia*, the producers are formulating dosage form methacholine chloride prior to and in anticipation of receiving prescriptions; the dosage form methacholine chloride is produced from tech grade bulk methacholine chloride that is not a component of any FDA-approved drug or FDA-sanctioned IND; the producers have not obtained written assurances that each lot of the bulk tech grade methacholine chloride has been made in an FDA-approved facility; the tech grade bulk methacholine chloride has not been guaranteed to meet official compendial requirements;

and, the methacholine chloride administered to patients is in essentially the same dosage form as Methapharm's methacholine chloride (Provocholine®) 100 mg/vial powder.

The tech grade suppliers know, have reason to know or reasonably could have anticipated that a substantial portion of their bulk methacholine chloride is being used by the unapproved formulators to produce non-FDA-approved dosage form methacholine chloride.

Analysis

As FDA is well aware, Section 127 of the FDA Modernization Act of 1997 amended the Act by adding section 503A (21 U.S.C. 353(a)), which provided certain conditions under which compounded drugs would be exempt from certain provisions of the Act including 21 U.S.C. §§ 352(f)(1) and 355. The United States Supreme Court struck down the solicitation and advertising restriction of 21 U.S.C. § 353(a) as an impermissible regulation of commercial speech. Because the unconstitutional restriction on commercial speech could not be severed from the rest of § 353(a), all of § 353(a) was invalidated. Accordingly, there are no exemptions from § 352(f)(1) or § 355 for compounded drugs.

Unapproved formulators of dosage form methacholine chloride are in violation of 21 U.S.C. §§ 331, 352, and 355, as set forth in greater detail below. Tech grade suppliers of bulk methacholine chloride are knowingly contributing to and inducing the unapproved formulators in the above violations. Moreover, tech grade suppliers are also violating 21 U.S.C. §§ 331, and 352. The general policy and specific factors contained in the Guidance for FDA Staff and Industry, Compliance Policy Guides Manual § 460.200, "Pharmacy Compounding" ("CPG") support FDA's exercise of its enforcement discretion here. There are also considerable public health risks associated with unapproved forms of methacholine chloride that support FDA's exercise of its enforcement action here.

1. **Violations by Unapproved Formulators of Dosage Form Methacholine Chloride**

   a. **Violation of 21 U.S.C. § 355(a).**

21 U.S.C. § 355(a) prohibits any person from "introduc[ing] or deliver[ing] for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) or (j) is effective with respect to such drug." Upon information and belief, unapproved formulators have introduced and continue to introduce into interstate commerce drug products containing methacholine chloride without an approval of an application pursuant to 21 U.S.C. § 355(b) or (j). The drug products containing methacholine chloride that these parties have introduced and continue to introduce into interstate commerce are drugs within the meaning of 21 U.S.C. § 321(g). These drug products are new drugs within the meaning of 21 U.S.C. § 321(p) because they are "not generally recognized...as safe and effective for use under the condition prescribed, recommended, or suggested in the labeling thereof...." 21 U.S.C. § 321(p). Thus, unapproved formulators are in violation of 21 U.S.C. § 355(a) and 331(d).

b. Violation of 21 U.S.C. § 352 Misbranding

Unapproved formulators of dosage form methacholine chloride are also in violation of 21 U.S.C. § 352 because the methacholine chloride products that they produce are misbranded under § 352 as they do not bear adequate directions for use. *See* 21 U.S.C. § 352 (stating that "[a] drug or device shall be deemed to be misbranded ... [u]nless its labeling bears (1) adequate directions for use"). As such, they are also in violation of 21 U.S.C. § 331(a)-(c) and (g).

c. Factors contained in Guidance for FDA Staff and Industry, Compliance Policy Guides Manual ("CPG") § 460.200 support FDA's exercise of its enforcement discretion.

Guidance for FDA Staff and Industry, Compliance Policy Guides Manual § 460.200 ("CPG") provides guidance in determining whether FDA will initiate enforcement action against pharmacies which purport to engage in the practice of pharmaceutical compounding. The general policy set forth in the CPG provides that FDA "should seriously consider enforcement action . . .when the scope and nature of a pharmacy's activities raise the kinds of concerns normally associated with a drug manufacturer and result in significant violations of the new drug, adulteration or misbranding provisions of the [Federal Food, Drug and Cosmetic Act]...." As set forth in parts (a) and (b) above, unapproved formulators are violating the new drug and misbranding provisions of the Federal Food, Drug and Cosmetic Act. Moreover, their

activities raise the kinds of concerns normally associated with a drug manufacturer. Thus, the general policy set forth in the CPG supports FDA enforcement action here.

A number of specific factors are also set forth in the CPG that support FDA enforcement action. They are as follows:

1) "Compounding" methacholine chloride without first receiving a valid prescription (CPG § 460.200 (1));
2) "Compounding" finished methacholine chloride from bulk methacholine chloride that is not a component of any FDA approved drug without an FDA sanctioned investigational new drug application (IND) in accordance with 21 U.S.C. § 355(i) and 21 CFR 312 § (CPG § 460.200(3));
3) Receiving, storing or using methacholine chloride before obtaining written assurance from the supplier that each lot of methacholine chloride has been made in an FDA-registered facility (CPG § 460.200(4));
4) Receiving, storing or using methacholine chloride not guaranteed or otherwise determined to meet official compendia requirements (CPG § 460.200(5)); and
5) "Compounding" methacholine chloride that is essentially a copy of Methapharm's Provocholine® (methacholine chloride) 100 mg/vial powder for solution, approved by FDA under NDA No. 19-193 (CPG § 460.200(8)).

Upon information and belief, unapproved formulators "compound" dosage form methacholine chloride in anticipation of receiving prescriptions. *See* CPG § 460.200 (1). Upon information and belief, unapproved formulators also "compound" dosage form methacholine chloride from bulk methacholine chloride that is not a component of any FDA approved drug without an FDA sanctioned IND in accordance with 21 U.S.C. § 355(i) and 21 CFR § 312. *See* CPG § 460.200(3). Upon information and belief, unapproved formulators receive, store and use methacholine chloride without obtaining written assurance from the supplier that each lot of methacholine chloride has been made in an FDA-registered facility. *See* CPG § 460.200(4). Upon information and belief, unapproved formulators receive, store and use methacholine chloride not guaranteed or otherwise determined to meet official compendia requirements. *See* CPG § 460.200(5). Upon information and belief, unapproved formulators further 'compound' methacholine

chloride that is essentially a copy of Provocholine.® *See* § 460.200(8). Thus, consistent with the specific factors set forth in the CPG, FDA should exercise its enforcement action here.

2. Violations by Tech Grade Suppliers of Bulk Methacholine Chloride

a. Tech grade suppliers are knowingly contributing to and inducing unapproved formulators in the above violations.

Upon information and belief, tech grade suppliers are supplying large quantities of unapproved bulk methacholine chloride to unapproved formulators with knowledge that the unapproved formulators will use the tech grade methacholine chloride to manufacture unapproved drug products which are then administered to patients. Thus, tech grade suppliers are knowingly contributing to and inducing unapproved formulators in the above violations. *See, e.g., United States v. Articles of Drug,* 825 F.2d 1238, 1246 (8th Cir. 1987) (stating that "[m]anufacturers and distributors may be held contributorily liable for the alleged violations of 21 U.S.C. § 352(i)(2) if they intentionally induced another to commit any such violation, or if they knew, had reason to know or reasonably could have anticipated that a substantial portion of their products would be passed off as controlled substances by others in the chain of distribution").

b. Violation of 21 U.S.C. § 352 Misbranding

Upon information and belief, tech grade suppliers are also in violation of 21 U.S.C. § 352 because the methacholine chloride products that they supply are misbranded under § 352 as they do not bear adequate directions for use. *See* 21 U.S.C. § 352 (stating that "[a] drug or device shall be deemed to be misbranded ... [u]nless its labeling bears (1) adequate directions for use").

The products are not exempt from 21 U.S.C. § 352 under 21 C.F.R. § 201.122, because the methacholine chloride is "intended for a use in manufacture, processing, or repacking which causes the finished article to be a new drug" and because no approved new drug application covers the production and delivery of the drug substance to the application holder by persons named in the application and because the methacholine chloride is not limited to investigational use only.

Upon information and belief, tech grade suppliers of bulk methacholine chloride are in further violation of 21 U.S.C. § 331(a) and (g), which prohibit respectively "[t]he introduction or delivery for introduction into interstate commerce of any ... drug ... that is ... misbranded" and "[t]he manufacture, within any Territory of any ... drug... that is ... misbranded."

3. Public Safety Concerns Regarding Use of Non-FDA Approved Forms of Methacholine Chloride Supporting Agency Action

There are numerous public health risks associated with administering to patients non-FDA approved forms of methacholine chloride produced with bulk methacholine chloride that is not subject to the same safeguards and controls as bulk materials used in FDA-approved drugs, which support FDA's exercise of its enforcement action here.

First, upon information and belief, a death occurred in June, 2001 at Johns Hopkins University after tech grade non-FDA approved methacholine chloride and hexamethonium were administered to a patient. Notably, in this instance, there was no disclosure in the patient consent form that non-FDA approved drugs were being administered.

Second, upon information and belief, there is a risk of cross-contamination in packaging and manufacturing facilities of non-FDA approved methacholine chloride. Such cross-contamination can cause allergic reactions in asthma patients who are susceptible to such reactions.

Third, there are no reporting requirement for adverse drug events using non-FDA approved tech grade methacholine chloride.

Fourth, upon information and belief, there is an increased risk of microbial levels of non-FDA approved bulk tech grade methacholine chloride creating lung infections.

Fifth, upon information and belief, there is a potential error in one of the compounding steps when bulk tech grade methacholine chloride is used due to hygroscopic nature of methacholine chloride that could affect drug safety and efficacy.

Sixth, upon information and belief, there is batch to batch variability with tech grade methacholine chloride as a result of tech grade material not being subject to the same controls and testing of FDA approved drugs.

Seventh, upon information and belief, methacholine chloride falls in the category of a high risk compounded sterile preparation as defined in the USP Chapter 797. This classification further evidences a public health risk associated with non-FDA approved tech grade methacholine chloride being used in pharmaceutical compounding.

4. FDA should order a recall of all methacholine chloride products that are in violation as set forth above.

21 CFR § 7.41 sets forth factors to consider for health hazard evaluations for products considered for recall as follows:

> (1) Whether any disease or injuries have already occurred from the use of the product;
>
> (2) Whether any existing conditions could contribute to a clinical situation that could expose humans or animals to a health hazard.
>
> (3) Assessment of hazard to various segments of the population, e.g., children, surgical patients, pets, livestock, etc., who are expected to be exposed to the product being considered, with particular attention paid to the hazard to those individuals who may be at greatest risk.
>
> (4) Assessment of the degree of seriousness of the health hazard to which the populations at risk would be exposed.
>
> (5) Assessment of the likelihood of occurrence of the hazard.
>
> (6) Assessment of the consequences (immediate or long-range) of occurrence of the hazard.

Many of the factors to consider for health hazard evaluation for products considered for recall favor initiating a recall in this instance. Upon information and belief, a death occurred in June, 2001 at Johns Hopkins University after tech grade non-FDA approved methacholine chloride and hexamethonium were administered to a patient. Upon information and belief, there is a risk of cross-contamination in packaging and manufacturing facilities of non-FDA approved methacholine chloride. Such cross-contamination can cause allergic reactions in asthma patients who are susceptible to such reactions. Upon information and belief, there is also an increased risk of microbial levels of non-FDA approved bulk tech grade methacholine chloride creating lung infections. The degree of seriousness of the health hazards associated with non-FDA approved tech grade methacholine chloride is evidenced most notably by the death that occurred at Johns Hopkins.

Factors considered in FDA's recall strategy are set forth in 21 C.F.R. § 7.42 as follows:

> (i) Results of health hazard evaluation.
>
> (ii) Ease in identifying the product.
>
> (iii) Degree to which the product's deficiency is obvious to the consumer or user.
>
> (iv) Degree to which the product remains unused in the market-place.
>
> (v) Continued availability of essential products.

A health hazard evaluation would support FDA recall here as set forth above. Upon information and belief, tech grade methacholine chloride that has been distributed to unapproved formulators and tech grade methacholine chloride that has been administered to patients would be easily identified by prescription records from unapproved formulators and by sales receipts from tech grade suppliers. Upon information and belief, the deficiency of dosage form methacholine produced from tech grade bulk methacholine chloride would not be obvious to a consumer. Upon information and belief, bulk tech grade methacholine supplied to the unapproved

formulators remains unused in the marketplace. Upon information and belief, FDA-approved methacholine chloride is readily available from Methapharm. Thus, the factors set forth in 21 C.F.R. § 7.42 support a recall in this case.

The factors set forth in 21 CFR § 7.45 covering FDA-requested recalls are as follows:

> (1) That a product that has been distributed presents a risk of illness or injury or gross consumer deception.
>
> (2) That the firm has not initiated a recall of the product.
>
> (3) That an agency action is necessary to protect the public health and welfare.

Upon information and belief, non-FDA approved dosage form methacholine chloride produced from bulk tech grade methacholine chloride presents a risk of illness or injury. Upon information and belief, no unapproved formulator of dosage form methacholine chloride or tech grade supplier of bulk methacholine chloride has initiated a recall of any methacholine chloride. Upon information and belief, there are numerous public health risks associated with the use of non-FDA approved forms of methacholine chloride as set forth in Part (B)(3), *supra,* that make Agency action necessary. Accordingly, an FDA-requested recall is appropriate in this instance.

5. Countervailing views.

Methapharm acknowledges its obligation to present countervailing arguments known to it. 21 C.F.R. § 10.30(b). Methapharm acknowledges that pharmacists have traditionally compounded reasonable quantities of human drugs following receipt of a valid prescription for an individual patient who requires a unique dosage form and/or strength and that FDA defers to state authorities regarding less significant violations related to pharmacy compounding. However, as set forth in CPG, "when the scope and nature of a pharmacies activities raise the kinds of concerns normally associated with a drug manufacturer and result in significant violations of the new drug,... or misbranding provisions of the Act, FDA has determined that it should seriously consider enforcement action." CPG § 460.200 at 3. In this case, FDA should take enforcement action. Methapharm is not aware of any other countervailing arguments.

6. Conclusion.

Methapharm requests immediate action as the public interest is substantially implicated. This Petition has conclusively shown that unapproved formulators of dosage form methacholine chloride are in violation of 21 U.S.C. §§ 331, 352, and 355. Tech grade suppliers of bulk methacholine chloride are knowingly contributing to and inducing the unapproved formulators in the above violations. Tech grade suppliers are also violating 21 U.S.C. §§ 331, and 352. The general policy and specific factors contained in the CPG support FDA's exercise of its enforcement discretion here. Moreover, the public health risks associated with unapproved forms of methacholine chloride provide further support for FDA's exercise of its enforcement action.

C. Environmental Assessment.

The actions requested by this Petition are subject to categorical exclusion pursuant to 21 C.F.R. § 25.30(a) – (c). No extraordinary circumstances exist to the applicant's knowledge In the alternative, based on the information discussed above, the proposed action requested in this petition will not significantly affect the quality of the human environment.

D. Economic Impact.

An Economic Impact Statement will be made at the request of the Commissioner.

E. Certification.

The undersigned certify, that, to the best knowledge and belief of the undersigned, this Petition includes all information and views on which the Petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the Petition.

Dated: December 23, 2004.

Respectfully submitted,

Michael J. Gaertner
Sara A. Lufrano
LORD, BISSELL & BROOK LLP
115 South LaSalle Street
Chicago, Illinois 60603
(312) 443-0700
(312) 443-0336 (facsimile)

Attorneys for Methapharm Inc.